## REMARKS

### The Amendments

The claims are amended to better conform them to U.S. practice and to address the 35 U.S.C. §112 rejections, as discussed below. Further, claims 77, 89 and 123 have been amended to recite that the drospirenone is used in the invention in micronized form; see, e.g., page 7, lines 14-32, of the specification. Claim 90 has been amended to recite oral administration.

The amendments do not narrow the scope of the claims and/or were not made for reasons related to patentability. The amendments should not be interpreted as an acquiescence to any objection or rejection made in this application. To the extent that the amendments avoid the prior art, competitors are warned that the amendments are not intended to and do not limit the scope of equivalents which may be asserted on subject matter outside the literal scope of any patented claims but not anticipated or rendered obvious by the prior art. Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

### Information Disclosure Statement

The Information Disclosure Statement filed herewith cites two references which were

cited by the Examiner of copending U.S. Ser. No. 09/654,227. This copending application, by the same inventors, is related to the instant application and may be of interest for the Examiner to consider. It should be noted that the Examiner has already indicated that the outstanding Office Action should not be a Final action, thus, the Information Disclosure Statement is being submitted under the terms of the Office Action not being Final.

**The Rejection under 35 U.S.C. §112, second paragraph**

The rejection of claims 77, 86-88, 100-102, 104, 105, 110-114, 116, 122 and 123-132 under 35 U.S.C. §112, second paragraph, are believed to be rendered moot, at least in part, by the above amendments and further in view of the following remarks.

Claim 77 is clarified as to the number of active agents, i.e., an estrogen and drospirenone.

As to the term "cycle" in claim 86, reference is made to the specification at page 3, line 9, where the term "per cycle" is defined as being from 21-31 days, typically 28 days. The cited text reads: *"in the present context, the term cycle itself or when associated with the term menstrual is intended to mean the number of days between menses in a woman. It can range from 21-31 days, typically 28 days*". In view of this definition in the specification and that one of ordinary skill in this art would clearly know the meaning of the term as used in these claims, it is urged that the term is definite.

As to the sequence of steps of administration in claims 104 and 105 (and claims 106-107 and 117-119), these claims have been amended so as to more clearly indicate the sequence of administering.

Claims 110-112 were objected to in view of the terms reciting continuous or sequential administration. It is respectfully submitted that a person of ordinary skill in the art would have no difficulties in interpreting the term "continuous administration" of estrogen and or drospirenone as being administration on a daily schedule for as long time as needed and "sequential administration" as having at least one gap of non-administration between two schedules of daily administration. One of ordinary skill in the art knows that sequential administration of progestogens (such as drospirenone) relates to conventional administration schemes used in the current state of the art of managing HRT. One of ordinary skill in the art also knows that sequential administration relates to administering the progestogen during one period of each cycle interrupted by one or two periods of no administering of said progestogen. Alternatively, the sequential administration relates to administering the progestogen for two separate periods within each cycle, interrupted by one period of no administering of said progestogen. As to claims 112, it is now rephrased to recite that the estrogen dosage is lower for the first 1 to 7 days after the last dosage of drospirenone is administered in the sequential period in comparison to the estrogen dosage administered before the start of sequential administration of drospirenone.

Similarly, as to the term "interrupted manner" in claim 113, it is submitted that one of ordinary skill in the art would know that the term "interrupted manner" in the context of administration a progestogen in managing HRT relates to several periods of administering the progestogen interrupted by periods of not administering the progestogen. Claim 114 recites a specific embodiment of the "interrupted manner" of administration relating to a "3-day-on-3-day-off-cycle." This terminology is believed to be self-evident and was even more clear to

one of ordinary skill in the art, i.e., it means administration was conducted for 3 straight days which was followed by 3 straight days without administration.

It is noted that the cited Elliesen reference discusses constant and intermittent modes of administration as well known in the art.

Claim 116 is clarified to recite that the treatment-free interval is 1 to 7 days, thus, addressing the objection thereto; see page 14, line 15, of the specification.

Claim 122 is clarified to recite that a dosage unit is administered for 1 to 12 cycles of 28 days. Thus, the term "cycle," which is known in the art and defined in the specification as discussed above, replaces "multiples of 28 days."

The objected to term "multiphased" in claims 123-132 is removed since it is unnecessary. This is despite that the term is sufficiently explained at page 10, lines 27 to 31, of the specification, reciting: *"In embodiments where the amount of DRSP and/or estrogen in the dosage unit varies according to the phase or day ..... such compositions, methods of treatments and preparations are termed multi-phased."*

The phrases "such as", "particular" and "in particular" are removed from amended claims 86-88, 100-102, 130 and 131.

For purposes of clarification, claim 90 has been amended to recite a method wherein the hormones are administered for at least one cycle of from 21 to 31 days. As such, it is more clear that the embodiments of claim 100 and 110 to 116 relate to the administration scheme within each cycle of 21 to 31 days.

For all of the above reasons, it is urged that the instant claims are definite for 35 U.S.C. §112 purposes when read in light of the specification and the knowledge of one of

ordinary skill in the art. Thus, the rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

**The Rejection under 35 U.S.C. §102 over Elliesen**

The rejection of claims 77-99 under 35 U.S.C. §102, as being anticipated by Elliesen (U.S. Patent No. 5,922,349) is respectfully traversed.

The objective of Elliesen is to provide a method and device for administering adjusted doses of a combination of an estrogen and an progestogen in managing HRT. The doses are delivered as extrudable compositions containing a plurality of non-discrete doses of an estrogen and a progestogen. The extrudable composition may be in the form of semi-solids and viscous liquids and is appropriate for topical, particularly transdermal, applications; see, e.g., col. 4, lines 5-35. The managing of HRT according to Elliesen relates to conventional administration schemes of administering an estrogen at least once daily, preferably without interruption, and administering progestogen during 12-14 days of each 28-day cycle. Optionally, the dosing regimen includes a treatment-free interval of 3-7 days in each treatment cycle or following 6 consecutive treatment cycles; see, e.g., cols. 13-14. The daily dosages of the estrogen are 0.5 to 4 mg and the daily dosages of drospirenone are 1-3 mg. Elliesen mentions drospirenone amongst 9 possible progestens; see col. 10, lines 16-28. But Elliesen provides no specific teaching of a composition or method using drospirenone; see Examples 1-3.

Elliesen does not teach the currently claimed compositions of independent claims 77 and 89 or claims dependent thereon reciting compositions containing drospirenone in

**micronised form**. Furthermore, Elliesen does not teach the current method of amended claim 90 reciting **oral administration** of an estrogen and drospirenone for at least one cycle.

Despite the recitation at col. 10, lines 16-28, it is urged that Elliesen does not fairly teach or suggest compositions or methods using micronized drospirenone as recited in applicants' claims. A comparison should be made between the section containing the listing of progestogens in the application text of Elliesen and in the corresponding international application (WO 97/11680; cited with the IDS here). Column 10, lines 16-28 of Elliesen reads:

> " *Examples of progestogen which can be employed in this invention (dosages are shown; transdermal dosages will vary therefrom in accordance with the absorption efficacy of the vehicle employed) are micronized*
> *progesterone (100-200 mg/day)*
> *northindrone acetate (0.5-2mg/day)*
> *norgestrel (80-250 meg)*
> *levonorgestrel(40-125 meg)*
> *gestodene (20-80 meg)*
> *CPA (1-2 mg/day)*
> *chlormadinone acetate (1-2 mg)*
> drospirenone *(1-3 mg)*
> *3-ketodesogestrel (40-120 meg)".*

WO 97/11680, lines 9-18, page 15, reads similarly, but in a different format:

> " *Examples of progestogen which can be employed in this invention (dosages shown are oral: transdermal dosages will vary therefrom in accordance with the absorption efficacy of the vehicle employed) are micronized progesterone (100-200 mg/day), norethisterone and ester, e.g. acetate (0.5-2mg/day), thereof, norgestrel (80-250 meg), levo-norgestrel(40-125 meg), chlormadinone acetate (1-2 mg), cyproterone acetate (1-2 mg/day), desogestrel, 3-ketodesogestrel (40-120 meg), drospirenone (1-3 mg), norgestimate, or gestodene (20-80 meg).*
> *Of these, gestodene, levo-norgestrel, 3-ketodesogestrel, drospirenone and - especially gestodene, levo-norgestrel and 3-ketodesogestrel are preferred".*

It is pointed out that the above-mentioned citation of the WO application applies the term "micronized" only to progesterone not the other progestens, such as drospirenone. It is respectfully urged that the printing format of the Elliesen patent gives the unwarranted impression that "micronized" applies to all the progestens. Also, the two last lines of the above-cited text of WO 97/11680 do not list drospirenone in micronized form, which further supports that the term micronized was only meant to apply to progesterone and not the other progestens. Moreover, we request the Examiner to study the progestogens listed in claim 12 of WO 97/11680 and US 5,992,349. These progestogens are not preceded by the word "micronised". On the contrary, the term "micronised" precedes the listed progesterones of claim 11. Finally reference is made to claim 11 of the Elliesen '349 patent wherein the "micronized" term is only associated with progesterone not the other progestens. Further, it is noted that the progesten used in the Examples 1-3 is not progesterone and is not micronized, thus, consistent with applicants' position. Accordingly, it is urged that the term "micronized" in Elliesen is only fairly read in connection with the use of progesterone and micronized drospirenone is not taught or suggested. Certainly, at least, there is not express teaching of micronized drospirenone in Elliesen, which would be required to support an anticipation rejection under 35 U.S.C. §102.

To further support applicants' position, it is pointed out that one of ordinary skill in the art at the time of the invention would have known that progesterone has a very poor solubility and needed to be furnished in micronised form for penetrating the skin and for being sufficiently absorbed into the circulating blood upon dermal administration. For example, the term, micronised progesterone, is referred to in the cited Uwe-Hollihn reference, page 91, third paragraph. This is again consistent with applicants' interpretation

that the inventors of US Pat. 5,92,349 did not intend to disclose that drospirenone is in micronised form but only progesterone because of its known poor solubility.

For the foregoing reasons, it is urged that Elliesen fails to anticipate instant claims 77, 89 and claims dependent thereon.

With regard to the independent method claim 90 and claims dependent thereon, we contend that Elliesen does not teach a method using a combination of an estrogen and drospirenone for treating deficient endogenous levels of estrogen, while at the same time providing protection of the endometrium from the adverse effects of estrogen nor such a method involving oral administration of the hormones.

Elliesen discusses oral administration only in passing at col. 11, lines 32-49, and col. 20, lines 44-59, the latter only in connection with methods for contraception not for HRT treatments. Elliesen's main objective regards HRT methods using formulations specifically adapted for topical application. It is stated at col. 11 that:

> *"it will be apparent for those skilled in the art that the principle upon which the invention is based can also be used in oral therapy by use of a suitable vehicle for the hormones."*

But no oral formulation comprising drospirenone is enabled by Elliesen. Certainly, there is no explicit teaching of a method involving oral administration of drospirenone and, therefore, can be no anticipation of applicants' claim 90. The present inventors were the first to provide an oral formulation effective in treating diseases and symptoms associated with menopause, despite that drospirenone is prone to conversion in the gastric fluid to its inactive isomer. For further proof on this point, see the Remarks and data discussed below in traversing the 35 U.S.C. §103 rejection.

Accordingly, it is urged that Elliesen fails to teach a method involving oral administration of an estrogen and drospirenone for HRT methods.

For the above reasons, it is urged that Elliesen fails to anticipate the instant claims and the rejection under 35 U.S.C. §102 should be withdrawn.

**The Rejection under 35 U.S.C. §102 over Lachnit**

The rejection of claims 77, 81-83, 86-90 and 123-131 under 35 U.S.C. §102, as being anticipated by Lachnit (U.S. Patent No. 5,756,490) is respectfully traversed.

Initially, it is noted that claim 84 was not included in this rejection. The substance of claim 84, i.e., the drospirenone being in micronized form, is now incorporated into independent claims 77, 89 and 123 (claim 123 reciting micronized or in a sprayed on form). Thus, it is believed that this rejection may be rendered moot, however, the following remarks on the reference will be made for completeness.

Lachnit relates to a preparation for hormonal contraception with two hormone components that are each physically separated in a packaging unit, in each case consisting of a number of daily dosage units that are placed physically separately. The first hormone component is a combination of an estrogen preparation and a progestogen preparation in either one phase or multiple structure; the second hormone component is an estrogen preparation. The first hormone component comprises 23 or 24 daily units and the second hormone component comprises 4 to 10 daily units. The claimed estrogens are 17β-estradiol, ethinyl estradiol and estradiol valerate. Drospirenone is suggested as one of 8 possible progestogens. There is no disclosure in the reference of any kind regarding micronised drospirenone or drospirenone in a form sprayed onto an inert carrier, particularly no specific

disclosure of such. Furthermore, Lachnit relates to a method of managing hormonal contraception, which applies to women with normal ranges of endogenous levels of estrogen. Thus, Lachnit does not apply to combining an estrogen and drospirenone in treating deficient endogenous levels of estrogen and to protect the endometrium from the adverse effects of estrogen.

For the above reasons, it is urged that Lachnit fails to anticipate the instant claims and the rejection under 35 U.S.C. §102 should be withdrawn.

**The Rejections under 35 U.S.C. §103**

The rejections of claims 77-132 under 35 U.S.C. §103, as being obvious over Elliesen, alone, or in view of Lachnit or further in view of the Uwe-Hollihn article are respectfully traversed.

The Elliesen and Lachnit references – and the deficiencies thereof in teaching applicants' invention – are discussed above and that discussion is incorporated herein by reference.

For the reasons discussed above, it is urged that Elliesen fails to teach compositions comprising or methods using micronised drospirenone. It also fails to suggest such. The teachings in Elliesen relating to micronized forms of compounds relates only to progesterone. There is no suggestion from the reference to micronize drospirenone.

Furthermore, Elliesen fails to teach or suggest hormone combinations, dosages and oral administration schemes applicable for a method of treating deficient endogenous levels of estrogen while at the same time protecting the endometrium from the adverse effects of the

estrogen by concurrent oral administration of drospirenone; see instant claim 90 and claims dependent thereon.

The present application relates, at least in part, to solving the problem of adverse effects on the endometrium as a result of hormone replacement therapy with an estrogen. The adverse effects on the endometrium may lead to hyperplasia of the endometrium, which further may result in cancer. According to the present invention, the protection of the endometrium from estrogen is accomplished, at least in part, by administering a proper dose of drospirenone orally during one or more treatment cycles. The inventors have also found that the proper dose of drospirenone to be administered per treatment period, e.g., of 28 days, is preferably in the range from about 15 to 70 mg.

The invention thus provides an effective treatment regimen in managing HRT by combining an estrogen (e.g. estradiol) and drospirenone. As mentioned above, the applicant provides additional data to further substantiate the teaching of the present application with respect to efficacy and adverse events of the treatment regimen (see Supporting Data A enclosed herein; which will be submitted in Declaration form when appropriate).

The additional Data A represents treatment regimens with oral continuous administering of 1 mg estradiol in combination with oral continuous administering of either 0.5, 1, 2, or 3 mg drospirenone, respectively. It was surprisingly found that the concurrent administration of drospirenone led to complete prevention of developing hyperplasia in comparison to women only administered 1 mg of estradiol (Supporting Data A, Example 4). Thus, the oral treatment regimen as disclosed in the present application is effective in replacing the deficient endogenous levels of estrogen in a woman without introducing the risk of developing hyperplasia.

Moreover, the present application relates, at least in part, to provide a reliable composition for oral administration, such that a high bioavailability of drospirenone is achieved despite of its low solubility and instability in acidic solution. It is namely known that at low pH, drospirenone is prone to isomeric conversion into an inactive form whilst, at higher pH values, drospirenone is degraded by hydrolysis. As may now be acknowledged by one of ordinary skill in the art, the low solubility of drospirenone in aqueous solution and the poor stability of drospirenone in acidic solution is likely to result in poor uptake of the drospirenone from the gastric-intestinal tract and potential loss of active form of drospirenone in the gastric fluid. Although, Elliesen mentions – without detail – possibilities for oral administration, it fails to mention to problems that would be faced in doing so with a poorly soluble form of drospirenone in aqueous solution. The present applicant provides herein an improved oral formulation of drospirenone with a high bioavailability, achieved, at least in part, by micronisation of drospirenone. However, as experienced by the present applicant, it would not have been obvious to provide an improved bioavailability of drospirenone by providing it in micronised form.

Applicants provide further supporting data to show the deleterious effect of micronisation on the stability of drospirenone (See Supporting Data B; this will be submitted in Declaration form when appropriate). The data show that at pH 1, the half-life for micronised drospirenone is as low as 30 minutes. Thus, 50% of the active form of drospirenone is converted into the inactive form after 30 minutes in gastric fluid. In comparison, only about 15% of non-micronised drospirenone is converted to its inactive form following exposure to acidic solution. Thus, a potential serious loss of active drospirenone would have been expected to occur in the gastric fluid, where the oral formulation,

disintegrated or partly disintegrated, resides until the gastric fluid is emptied into the upper part of the intestinal tract. The gastric emptying time depends on various factors, e.g. fed state or not fed state. In general the residence time may be up to several hours. Hence, the potential conversion of drospirenone into its inactive form is expected to be a serious problem whenever an oral formulation for delivery of drospirenone in the gastric fluid is desirable. This conversion was expected to be exacerbated by micronisation.

The Supporting Data B shows in vitro dissolution studies that compare the behavior of micronised and non-micronised drospirenone using test conditions that simulate the conditions in the gastric-intestinal tract. The dissolution medium is kept at a pH of 1 for about 90 minutes followed by a change in pH to about 7 after 90 minutes of dissolution testing, where after the test continues at pH 7. This set-up mimics the *in-vivo* conditions with a residence time in the gastric fluid for about 90 minutes and subsequent emptying the oral formulation into the intestinal tract where the pH is about 7. These studies show that about 90% of the micronised drospirenone is dissolved after 30 minutes (Supporting Data B, figure 1). However, unfortunately (and significantly) almost 40% of the total amount of drospirenone has concurrently been converted to its inactive form. In the case of the non-micronised form, about 40% of the total amount is dissolved after 30 minutes (Supporting Data B, figure 2). However, only 15% of the total amount of drospirenone is converted into the inactive isomer in acidic solution. Thus, less drospirenone is dissolved from the formulation comprising the non-micronised drospirenone and less drospirenone is degraded in acidic fluid. Hence, a greater amount of drospirenone is available for absorption in the intestine. Thus, these *in vitro* data teaches the skilled person that micronization would not favor bioavailability.

Further, as seen from the dissolution curves (Supporting Data B, figure 3) for the formulation comprising the non-micronised form, about 45 % of the active drospirenone is present after 360 minutes in the dissolution media at pH 7. In comparison, only about 25 % of the active drospirenone is present from the dissolution of the micronised form. These *in vitro* data again teaches the skilled person that micronization would not favor bioavailability.

In summary, the above data shows that using drospirenone in micronised form for the preparation of an oral formulation would have been expected to lead to poor bioavailability. In fact the data teaches that the use of non-micronised form may ensure higher bioavailability than obtainable with the micronised form, since more drospirenone is available for the absorption in the intestine. Thus, one of ordinary skill in the art would not be directed to develop a formulation comprising micronised drospirenone, in particular with reference to the enormous expenses needed for conducting clinical trials in order to have new products approved by health authorities. Although one of ordinary skill in the art could have attempted to increase the bioavailability of drospirenone using micronization, he would not have been motivated to do so and expect a favorable outcome. He would instead have expected micronization to increase the rate of degradation of drospirenone and thus not improve (and perhaps be deleterious to) the bioavailability of the compound.

Applicants' invention contributes significantly to the state of the art by making it possible to provide an oral formulation of drospirenone with a high bioavailability and efficacy in preventing the endometrium from developing hyperplasia. As can be seen from the Supporting data A, the absolute bioavailability of the oral formulation according to the invention is about 76% and the relative bioavailability of the oral formulation in comparison to an oral suspension is about 102% (Supporting Data A, example 2). In the present

invention, the high bioavailability of drospirenone has been achieved despite its poor solubility and lack of stability in aqueous solutions at various pH values.

Based on the above, it would not have been obvious from Elliesen to use micronised drospirenone for improving its bioavailability upon oral administering of drospirenone nor is it obvious to predict the proper doses of estrogen and drospirenone upon oral administration so that the symptoms associated with deficient levels of estrogen is effectively treated and the endometrium is prevented from developing hyperplasia. Thus, the 35 U.S.C. §103 rejection over Elliesen alone should be withdrawn.

As to the combined teachings of Elliesen with Lachnit, Lachnit teaches nothing regarding micronized forms of drospirenone and, thus, cannot make up for the deficiencies of Elliesen and/or rebut the Supporting Data provided by applicants.

Further, Lachnit teaches a method for inhibiting ovulation by administering a low dose of estrogen in combination a gestagen such as drospirenone. It is explicitly stated that the dose and frequency of administering the gestagen (drospirenone) is evident for achieving inhibiting of ovulation and lower incidences of breakthrough ovulation's. These teachings relating to sufficient doses of drospirenone for inhibiting ovulation will not be able to predict the proper dosing regimen for effectively protecting the endometrium from hyperplasia. Lachnit fails to recognize the problem of hyperplasia. For these reasons, it is urged that the combination of Lachnit with Elliesen also fails to render the claimed invention obvious under 35 U.S.C. §103.

As to the further rejection citing the Uwe-Hollihn article in combination with Elliesen and Lachnit, the article provides no teachings regarding micronised drospirenone nor the result of protecting the endometrium against hyperplasia. Therefore, Uwe-Hollihn fails to fill

the missing teachings from the combination of Elliesen and Lachnit and the combined teachings of all three references are deficient in suggesting applicants' invention on these elements. Accordingly, the final rejection under 35 U.S.C. §103 should also be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

Respectfully submitted,

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**77. (Amended Twice)** A pharmaceutical composition comprising:

~~as a first active agent,~~ i) an estrogen ~~(or naturally or synthetic derivative thereof)~~ in a sufficient ~~amounts~~ amount to treat diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women~~, and~~;

~~as a second active agent, 6β,7β;15β;16β-dimethylene-3-oxo-17α-preg-4-ene-21,17-carbolactone (~~ ii) drospirenone~~)~~ in micronised form and in a sufficient ~~amounts~~ amount to protect the endometrium from the adverse effects of estrogen~~,~~; and

~~together with~~ iii) a pharmaceutically acceptable excipient or carrier.

**86. (Amended)** A composition according to claim 77, wherein the dose of ~~DRSP~~ drospirenone corresponds to 15 to 70 mg per cycle.

**87. (Amended)** A composition according to claim 77, wherein the amount of ~~DRSP~~ drospirenone corresponds to a daily dose ranging from 0.25 to 10 mg~~, such as about 0.25 to 8, 0.25 to 6, 0.25 to 5, 0.5 to 4.5, 1 to 4, and 1.5 to 3.5 mg~~.

**88. (Amended)** A composition according to claim 83, wherein the amount of estradiol corresponds to a daily dose ranging from 0.1 to 5 mg~~, such as about 0.2 to 4.5, 0.5 to 4, 1 to 3, in particular 1, 2, or 3 mg~~.

**89. (Twice Amended)** A pharmaceutical composition comprising:

i) ~~as a first active agent~~ estradiol in ~~amounts~~ an amount corresponding to a daily dose of 1 to 3 mg to treat diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women,

ii) ~~and as a second active agent 6β,7β;15β;16β-dimethylene-3-oxo-17α-preg-4-ene-21,17-carbolactone (~~drospirenone~~)~~ in micronised form and in ~~amounts~~ an amount corresponding to a daily dose of 1 to 3.5 mg to protect the endometrium from the adverse effects of estrogen, and

iii) ~~together with~~ a pharmaceutically acceptable excipient or carrier.

**90. (Amended)** A method of treating and preventing diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women comprising administering for at least one cycle of from 21 to 31 days;

an estrogen in a sufficient ~~amounts~~ amount to alleviate said diseases, disorders and symptoms,

and drospirenone in a sufficient ~~amounts~~ amount to protect the endometrium from adverse effects of estrogen,

said administering being by oral means.

**97. (Amended)** A method according to claim 90, wherein drospirenone ~~(DRSP)~~ is in micronized form.

**100. (Amended)** A method according to claim 90, wherein the dose of drospirenone corresponds to 15 to 70 mg per cycle~~, such as 20 to 60 mg per cycle, particularly 40 to 60 mg~~

~~per cycle~~.

**101. (Amended)** A method according to claim 90, wherein the amount of drospirenone corresponds to a daily dose ranging from 0.25 to 10 mg~~, such as about 0.25 to 8, 0.25 to 6, 0.25 to 5, 0.5 to 4.5, 1 to 4, and 1.5 to 3.5 mg~~.

**102. (Amended)** A method according to claim 96, wherein the amount of estradiol corresponds to a daily dose ranging from 0.1 to 5 mg~~, such as about 0.2 to 4.5, 0.5 to 4, 1 to 3, in particular 1, 2 or 3 mg~~.

**104. (Amended)** A method according claim 90, comprising:

a first treatment period of ~~administering for~~ 10 to 12 days comprising administering a daily dosage unit comprising estradiol in an amount ~~amounts~~ corresponding to a daily ~~doses~~ dose ranging from 0.1 to 5 mg; ~~and~~

following the first treatment period, a second treatment period of ~~administering for~~ 10 to 12 days comprising administering a daily dosage unit comprising estradiol in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.1 to 5 mg and drospirenone in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.25 to 6 mg; and

following the second treatment period, a third treatment period of ~~administering for~~ 4 to 8 days comprising administering a daily dosage unit comprising estradiol in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.25 to 5 mg.

**105. (Amended)** A method according claim 90, comprising:

a first treatment period of ~~administering for~~ 10 to 12 days comprising administering a daily dosage unit comprising estradiol in an amount ~~amounts~~ corresponding to a daily ~~doses~~ dose ranging from 0.1 to 5 mg; ~~and~~

following the first treatment period, a second treatment period of ~~administering for~~ 10 to 12 days comprising administering a daily dosage unit comprising estradiol in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.1 to 5 mg and drospirenone in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.25 to 6 mg; and

following the second treatment period, a third treatment period of ~~administering for~~ 4 to 8 days comprising administering a daily dosage unit ~~comprising~~ of a placebo or blank.

**106. (Amended)** A method according to claim 90, comprising:

a first treatment period of ~~administering for~~ at least 21 days comprising administering a daily dosage unit comprising estradiol in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.1 to 5 mg and drospirenone in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.25 to 6 mg; and

following the first treatment period, a second treatment period of ~~administering for~~ no more than 7 days comprising administering a daily dosage unit ~~comprising~~ of a placebo or blank.

**107. (Amended)** A method according to claim 90, comprising:

a first treatment period of ~~administering for~~ at least 21 days comprising administering a daily dosage unit comprising estradiol in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.1 to 5 mg and drospirenone in ~~amounts~~ an amount corresponding to a

daily ~~doses ranging~~ dose of from 0.25 to 6 mg; and

following the first treatment period, a second treatment period of ~~administering for~~ no more than 7 days comprising administering a daily dosage unit comprising estradiol in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.1 to 5 mg.

**112. (Amended)** A method according to claim 111, wherein the estrogen dosage is lower for the first 1 to 7 days immediately ~~following~~ after finalizing said sequential administration of drospirenone.

**116. (Amended)** A method according to claim 90, wherein the estrogen and the drospirenone are each administered sequentially with a treatment-free interval of 1-7 days within each cycle.

**117. (Amended)** A method according to claim 90, comprising:

a first treatment period of administering for 20 to 24 days a daily dosage unit comprising estradiol in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.1 to 5 mg, and drospirenone in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.25 to 6 mg for the last 10 to 12 days of said 20 to 24 days, and

following the first treatment period, administering for 4 to 8 days a daily dosage unit comprising no active ingredient.

118. **(Amended)** A method according to claim 90, comprising:

a first treatment period of administering for 20 to 24 days a daily dosage unit

comprising estradiol in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.1 to 5 mg, and drospirenone in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.25 to 6 mg for the last 10 to 12 days of said 20 to 24 days, and

following the first treatment period, administering for 4 to 8 days a daily dosage of unit comprising estradiol in ~~amounts~~ an amount less than daily dosage unit taken for said 20 to 24 day administration of estradiol.

**119. (Amended)** A method according to claim 90, comprising:

a first treatment period of administering for 20 to 24 days a daily dosage unit comprising estradiol in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.1 to 5 mg, and drospirenone in ~~amounts~~ an amount corresponding to a daily ~~doses ranging~~ dose of from 0.25 to 6 mg for the last 10 to 12 days of said 20 to 24 days, and

following the first treatment period, not administering any dosage units for 4 to 8 days.

**122. (Amended)** A method according to claim 104, wherein the daily dosage units are administered for 1 to 12 cycles~~, preferably 2 to 8, such as 2, 3, 4 5, 6, 7, and 8 multiples~~ of 28 days per cycle.

**123. (Amended)** A ~~multi phased~~ pharmaceutical ~~preparation~~ composition consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of at least 21 days wherein said daily dosage units comprise a combination of estradiol in an amount ranging from about

0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg, the drospirenone being in micronized form or sprayed from a solution onto particles of an inert carrier.

**124. (Amended)** A ~~multi-phased~~ pharmaceutical ~~preparation~~ composition according to claim 123 consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 28 days.

**125. (Amended)** A ~~multi-phased~~ pharmaceutical ~~preparation~~ composition according to claim 124 consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 28 days, wherein at least 21 said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and

no more than 7 said dosage units comprise a placebo or a blank.

**126. (Amended)** A ~~multi-phased~~ pharmaceutical ~~preparation~~ composition according to claim 124, wherein at least 21 said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and

no more than 7 said dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg.

**127. (Amended)** A ~~multi-phased~~ pharmaceutical ~~preparation~~ composition according to claim 124, wherein at least 10 said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg; and

at least 10 said daily dosage units ~~comprises~~ comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and

no more than 8 of said daily dosage units comprise a placebo or blank.

**128. (Amended)** A ~~multi-phased~~ pharmaceutical ~~preparation~~ composition according to claim 124, wherein at least 10 said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg; and

at least 10 said daily dosage units ~~comprises~~ comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and

no more than 8 of said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg.

**129. (Amended)** A ~~multi-phased~~ pharmaceutical ~~preparation~~ composition according to claim 123, consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 21 to 30 consecutive days,

wherein 10 to 15 said daily dosage units comprise a combination of estradiol in an amount

ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and

10 to 15 said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg.

**130. (Amended)** A ~~preparation~~ pharmaceutical composition according to claim 123, wherein the number of daily dosage units is at least 21 or a multiple of 21 ~~such as 2 to 12, particularly 2 to 8, such as 2 to 6~~.

**131. (Amended)** A ~~preparation~~ pharmaceutical composition according to claim 123, wherein the number of daily dosage units is 28 or a multiple of 28 ~~such as 2 to 12, particularly 2 to 8 such as 2 to 6~~.

**132. (Amended)** A ~~preparation~~ pharmaceutical composition according to claim 123, wherein said daily dosage units comprise estradiol ~~and/or drospirenone~~ in micronized form or sprayed from a solution onto particles of inert carrier.

Application No: 09/757,688
Art Unit: 1615
Inventor: Heil et al.
Schering Aktiengesellschaft
Drospirenone for Hormone replacement therapy

**SUPPORTING DATA A**

Supporting Data A relates to clinical documentation on the efficacy and adverse events from continuous-combined hormone replacement therapy by daily administering of tablets containing 1 mg estradiol and 2 mg drospirenone.

The data presented data herein supports the present Examples in the above-mentioned application with regard to bioavailability, efficacy against hot flushes, osteoporosis and hyperplasia:

**Example 2. Bioavailability**
The bioavailability was investigated as outlined in Example 2 in the present application.

*Results:*
The absolute bioavailability of drospirenone was determined to be 76 ± 13% after oral administration of 2 mg drospirenone and 85 ± 22% after oral administration of a microcrystalline suspension containing 3.13 mg drospirenone.

The relative bioavailability of drospirenone from tablets containing 1 or 3 mg drospirenone together with 1 mg E2 was 102 and 104%, respectively, compared to a microcrystalline suspension.

**Example 4.: Endometrial Protection**
The efficacy on endometrial protection of estradiol 1 mg and various doses of drospirenone was investigated as outlined in Example 4 in the present application.

*Results*
Neither hyperplasia nor cancer was found in any of the biopsies obtained from women in medication with the combined therapy, estradiol and drospirenone. Specific results are shown in table 1:

Table 1. Endometrial biopsy results based on endometrial thickness and diagnoses relates to hyperplasia

| | 1mg E2<br>n (%) | 1mg E2 + 0.5mg DRSP<br>n (%) | 1mg E2 + 1mg DRSP<br>n (%) | 1mg E2 + 2mg DRSP<br>n (%) | 1mg E2 + 3mg DRSP<br>n (%) |
|---|---|---|---|---|---|
| Proliferative endometrium | 21.3 | 8.9 | 6.3 | 4.6 | 4.1 |
| Simple hyperplasia without cytological atypia | 8.6 | 0.0 | 0.0 | 0.0 | 0.0 |
| Complex hyperplasia without cytological atypia | 0.5 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

| | | | | | |
|---|---|---|---|---|---|
| Atypical hyperplasia | 0.5 | 1 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Cancer | 0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

n = number of subjects in %.

**Example 5:. Osteoporosis Prevention**

The prevention of osteoporosis of estradiol 1 mg and various doses of drospirenone was investigated as outlined in Example 5 in the present application.

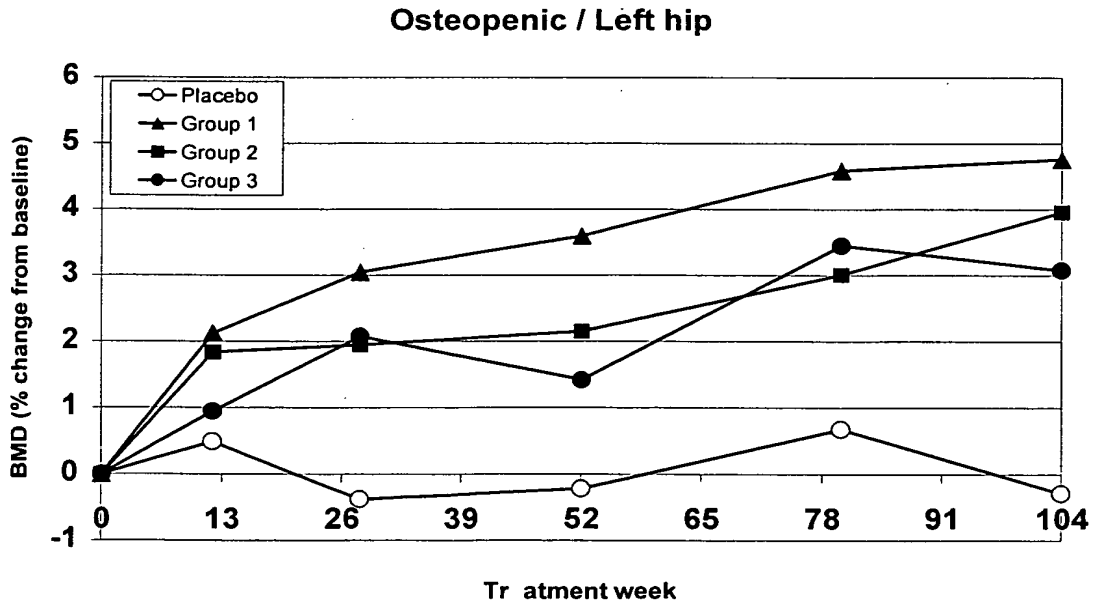
*Results*

Treatment with any of the three Estradiol/Drospirenone combinations, 1mg Estradiol with 1, 2 or 3 mg drospirenone, increased left hip Bone Mass Density (BMD) in osteopenic patients by a mean 3.1% to 4.8% of baseline, compared to a mean decrease of 0.3% for placebo treatment. In non-osteopenic patients, a decrease in left hip BMD of 0.6% for placebo and an increase of 2.8 to 2.9% for the active treatments were observed. The differences in the % change of left hip BMD between each active treatment and placebo treatment were statistically significant. During treatment with the E2/DRSP combinations, 52 of the 54 women in the osteopenic subgroup (96%) and 67 of the 77 women in the non-osteopenic subgroup (87%) gained or maintained BMD in the hip.

Overall, the data showed an increase in BMD during treatment with any of the three E2/DRSP combinations compared to a decrease during treatment with placebo

The BMD data for the most relevant regions, left hip and lumbar spine L1-L4, during the two-year treatments are summarized in figure 1:

Figure 1. Average percent change from baseline in left hip and lumbar spine BMD in osteopenic and non-osteopenic patients



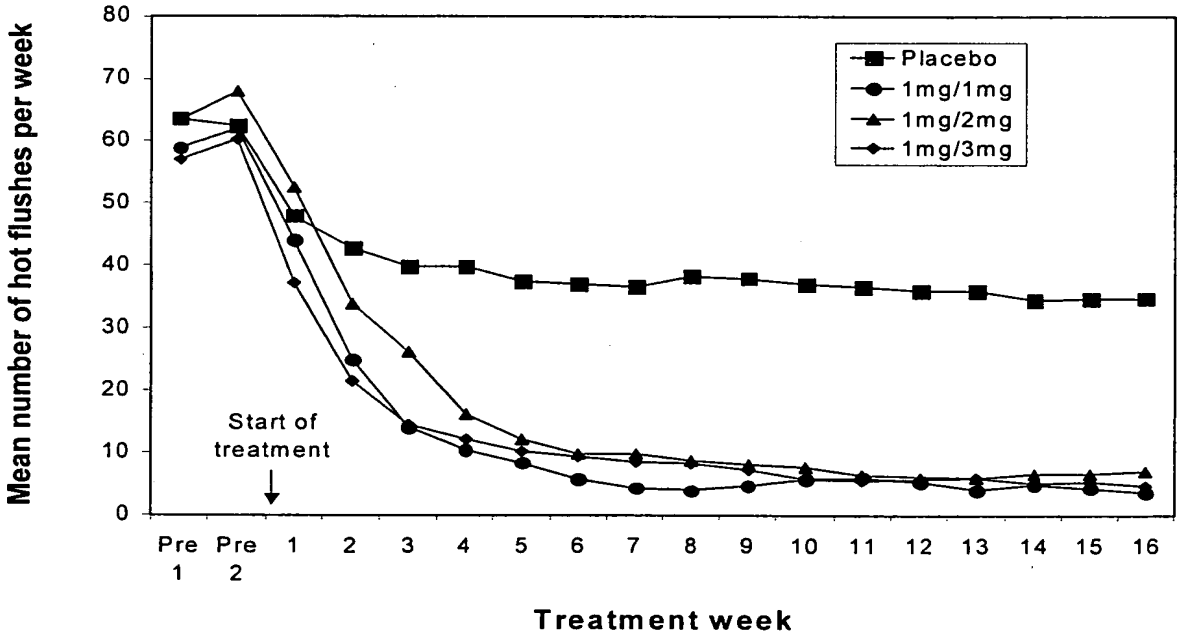

Group 1: 1 mg estradiol + 1 mg drospirenone
Group 2: 1 mg estradiol + 2 mg drospirenone

Group 3: 1 mg estradiol + 3 mg drospirenone

**Example 6: Menopausal Symptoms (Hot Flushes)**
The efficacy of estradiol 1 mg and various doses of drospirenone on reducing hot flushes was investigated as outlined in Example 6 in the present application.

*Results*
The mean number of hot flushes dropped from around 60 per week at baseline by 45% during treatment with placebo, and by 90%, 87%, and 86% respectively during treatment with the combinations of 1 mg E2 with 1, 2, and 3 mg DRSP. The differences between each active treatment and placebo were statistically significant. The maximum treatment effect was almost achieved after five treatment weeks, see the following figure 2.

Figure 2. Mean number of hot flushes per patient per week



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**SUPPORTING DATA B**

Supporting Data B contains data from the comparative investigation of the in vitro dissolution of micronised drospirenone versus non-micronised drospirenone under dissolution conditions simulating the in vivo conditions of the gastric fluid and intestinal fluid.

**Experimental Setup**:

| | |
|---|---|
| Dissolution method: | USP Paddle method 2 |
| Dissolution medium 1: | 900 ml of 0.1 N HCl |
| Dissolution medium 2: | 900 ml of 0.1 N HCl is mixed with boric acid/KCl buffer pH 10 to adjust the pH to 7. |
| Stirring rate: | 50 rpm. |

Dissolution medium 1 is applied for the first 90 minutes, followed by dissolution media 2 for the next time period up to 1440 minutes after initiating the dissolution testing. Thus, the dissolution conditions in question simulate the in vivo conditions; where the oral formulation disintegrates from a tablet or a pill or is released from a capsule and drospirenone initiates dissolution in the gastric fluid. Then, the released or disintegrated formulation and any dissolved drospirenone may reside in the gastric fluid for up to 90 minutes until the gastric content is emptied into the intestine where the pH is about 7.

**Results:**

The results is shown by figures 1, 2, and 3. Please notice that upon reading the figures 1 to 3, the pH is 1 within the first 90 minutes and pH is 7 within the next 90 to 360 minutes.

Figure 1: Dissolution of **micronised** drospirenone from an oral formulation .The total amount dissolved (sum of active and inactive form of drospirenone) as well as the individual amount of the active form and the inactive form in the dissolution medium is shown.

Figure 2: Dissolution of **non-micronised** drospirenone from an oral formulation .The total amount dissolved (sum of active and inactive form of drospirenone) as well as the individual amount of the active form and the inactive form in the dissolution medium is shown.

Figure 3: Comparison of the dissolution of oral formulation comprising either **micronised or non-micronised** drospirenone. The amount of the active drospirenone is shown.

**Figure 1.**
**Dissolution of micronised Drospirenone (DRSP) from an oral formulation**

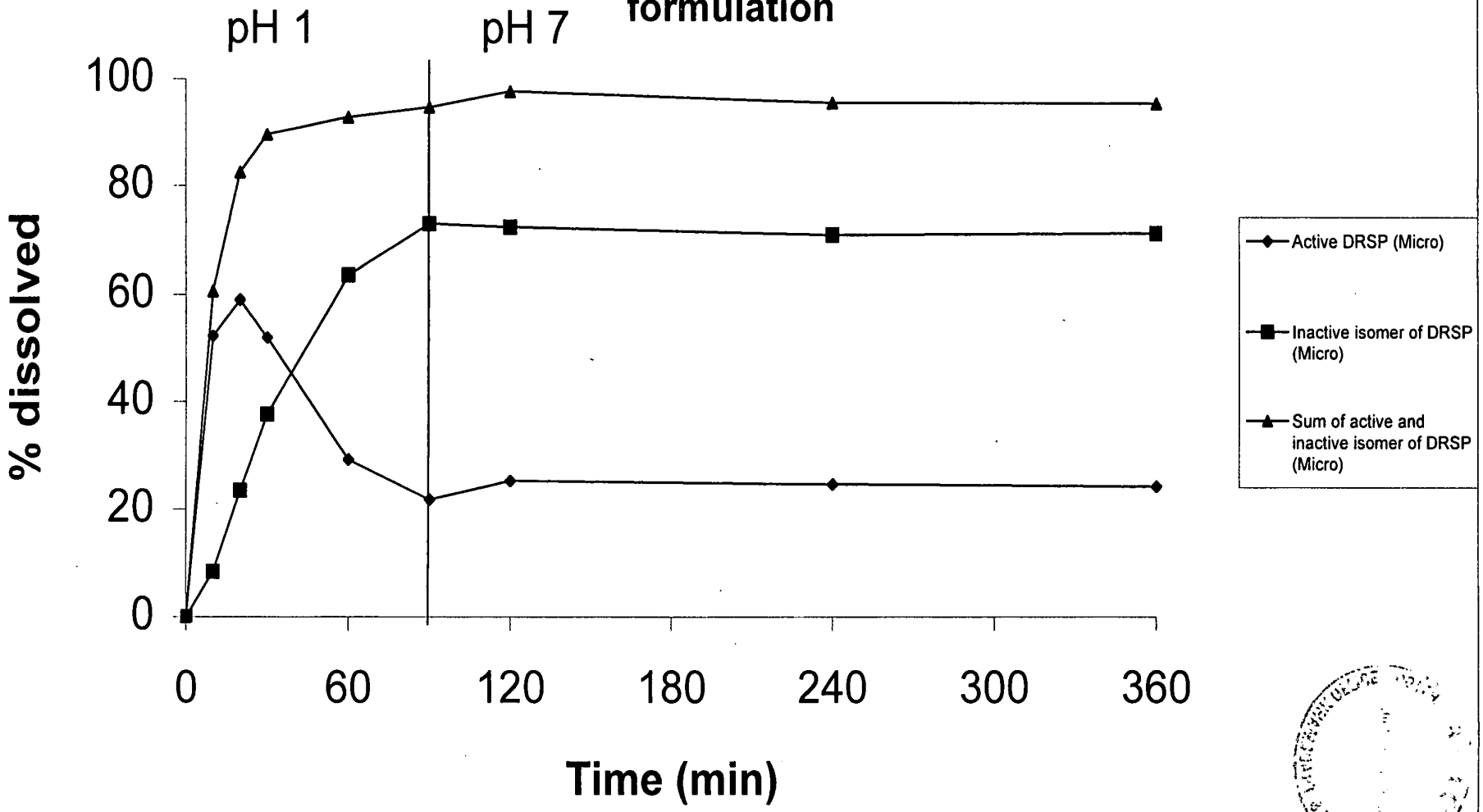

**Figure 2**

**Dissolution of non-micronised Drospirenone (DRSP) from an oral formulation**

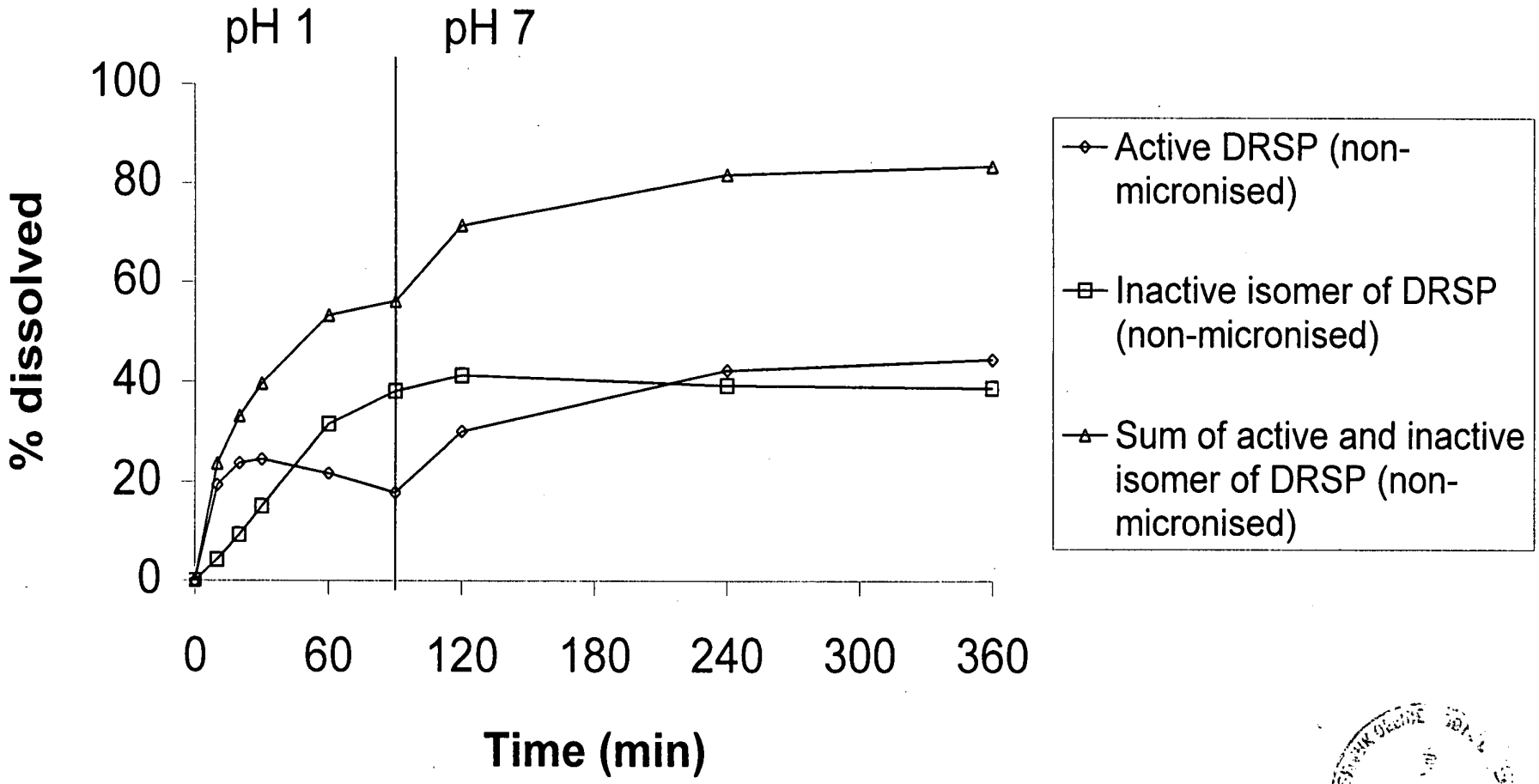

**Figure 3**
**Comparison of dissolution profiles of micronised and non-micronised Drospirenone (DRSP)**